NKDEP

National Kidney Disease
Education Program

Lab Working Group Call
10/18/04

Participants:
John Eckfeldt, Chair, University of Minnesota
Elisa Gladstone, NIDDK
Tom Hostetter, NIDDK
Glen Hortin, NIH
Andy Levey, Tufts University
Greg Miller, Virginia Commonwealth University
Gary Myers, CDC

Guests:
David A. Armbruster, Abbott Laboratories
Georgia Jeffs Kaplan

Review Draft of Manuscript:

- For authorship of the article, all contributors will be listed. The NKDEP Lab Working Group also will be named.
- Gary Myers will circulate to the entire group a list of authors that have contributed to the manuscript, and members can respond if they think they should be included.
- Gary will draft an abstract after the manuscript draft is completed.
- A list of non-standard abbreviations will be needed.

Manuscript Revisions:

- Page 14, Greg Miller asked: *Is clearance really done for dose adjustment purposes or is calculated GFR used?*
- The current sentence reads: *Clearance measurements should be performed if more precise knowledge of the GFR is necessary, such as evaluation of kidney transplant donors, dosage adjustment for highly toxic medications that are excreted by the kidneys (high-dose methotrexate), or studies of progression of kidney disease (especially in individuals with GFR >60 ml/min/1.73 m^2).* Gary will modify this sentence and replace "should be" and say that people with abnormal bodies may need a 24-hour urine collection.
- Andy Levey commented that this section on GFR interrupted the flow of the manuscript. There was consensus to put the section on "Clinical laboratory-based analytical systems for measuring serum creatinine to assess GFR" after the section on GFR.
- There was also consensus to put the section on biological variability ahead of the section on analytical specifications.

- There was agreement to move the section on methods to measure creatinine after the analytical specifications for GFR. Then all the GFR information will be in one place before the analytical specifications.
- GFR should go after the section on biological variability, then performance specifications then details on the specifications and problems. Work on the lead-in and the flow for these sections to get the transitions right.
- Andy said he would review the document after Gary rewrites it. He suggested keeping the performance specifications for GFR with the bio-variability ahead of the clinically based analytic systems.
- The next discussion concerned the comment on page 19 of the draft document on whether or not a section should be added on analytical non-specificity bias. Mauro Panteghini's comments address this issue and give references and data from his lab saying this is still a problem. Greg Miller said it is important to note that if the imprecision is down, if the analytical non-specificity bias is still there you can still get GFR errors. We should pose this issue, he said, and make a recommendation. Laboratory medicine needs to address this issue. We should discuss this and list it as a limitation. We can standardize but the non-specificity issue remains. The Working Group should make a recommendation. Reagent costs will rise if we convert to enzymatic methods. We can't make a strong recommendation now. Dr. Armbruster said there would be an impact on manufacturers. He agreed that the Lab Group should make a point that even if you standardize the assay, the manufacturers must account for the inherent non-specificity bias. Standardization is not necessarily a panacea. Greg said that readers must understand that reducing imprecision and doing standardization may still result in false positives because estimated GFR is only a screening tool.
- Gary said after the section on resources for standardization, part of this information on analytical non-specificity bias could be placed. Linda Theinpont and Dietman Stocke had a paper in the European Journal of Biochemistry that could be used as a reference. It compared ID-MS vs. Jaffe, etc. We could also add Mauro's references here. There was one in Clinical Chemistry in 2004. Gary will work on this and Greg will review it.
- Page 26: There was consensus to delete the sentence: *The overall range of method specific bias in the serum creatinine range 2 to 4 mg/dL are not as well studied.*
- John said Mauro's comments are non controversial. There is a section on intra individual variability and the changes he suggests are good although the flow is bad.
- Greg said the way bio-variability is presented is problematic: There is good information on creatinine mixed with information on creatinine clearance, which is mixing apples and oranges on the underlying biologic variability. We are not measuring creatinine clearance. Some sentences seem contradictory. The biggest problem is: Is it appropriate to include biological variability from creatinine clearance to biological variability of creatinine and the impact on clearance. John said we want a link of creatinine to GFR, but there may be little published data on intra-individual biological variability of GFR.
- Greg said page 11 is a telling statement on creatinine and individual variability and biological variability. Even in the Conclusions and the Recommendations the two biological levels of variability make it confusing. Andy said if we include the biological variability of creatinine clearance we should focus on the bio-variability of GFR. Greg said we use the creatinine clearance estimate interchangeably with the bio variability of GFR. Greg has highlighted all the places this appears in the text. Andy said if you want bio variability of creatinine clearance with the bio variability of GFR that seems to say one reflects the other but it really

only reflects the variability in urine collection, which is why we don't want to do creatinine clearance. Greg will send these comments to Gary.

Suggested changes and additions to RECOMMENDATIONS:

- The first comment was that the manuscript contains no recommendation on using 2 decimal places. We need to report values to two decimal places. Throughout the manuscript it says to use one decimal place like 1.0. We should make that recommendation two decimal places in the document. In the Modification of Diet in Renal Disease (MDRD) study if the flow values were under 1.0 they were reported to one decimal place but with two digits. The NKF/NKDEP Consensus Conference said to report creatinine to two decimal places if less than 1; so not 5.02 vs. 5.01 but .92 instead of .9. It is important at the low values. Explain that the gain in precision will be in the low numbers. MDRD was one decimal point but two digits. There was consensus that this was a good point.
- There was consensus that the document needs to contain SI units, perhaps in parentheses.
- Greg said we don't mention ID-MS. We go through routine methods and we need a paragraph saying ID-MF is the highest order available. Put it on page 10 after HPLC. Or we could add it on page 33 in the reference methods section at the beginning of the clinical laboratory-based section and expand to why people like IDMF**.** They like isotope dissolution. Put it in a section called ID-MS within the section on methods and add information on LCMS. GC is being replaced by LC in many laboratories. Mauro mentioned there has been one ID LCMS reference method for creatinine submitted to JCTLM, but it is not yet approved. Mauro attached a paper by O'Connor. Put this section on isotope dilution methods after the HPLC section.
- Greg said we don't state the abbreviated MDRD equation anywhere. We should be careful to state that it was based on the kinetic Jaffe method. Andy said: Put it in as a table or a box then qualifications can go in a legend or in a footnote. There was some discussion of referencing the NKDEP website with the MDRD equation on it; however there was a concern that *Clinical Chemistry* may not like to reference websites so the equation information should go in as a box. Table 1 on page 30 references a website; it might be better to cite the paper that describes it instead. Andy said eliminate the second part of this table on GFR. Keep creatinine on the top so you can eliminate this table. You are referencing a commercial website. Gary will check the citations and get rid of the second half of the table. The top half of the table may already be referenced. Gary will check to see if the references are there.
- There was consensus to remove the direct reference to the Vitros method in the text.

CONCLUSIONS/LIMITATIONS/RECOMMENDATIONS

- Stability and difference specimens: we need a sentence on creatinine stability for those doing frozen samples or materials that stand around for a few days. John said they did some freeze/thaw and plasma serum tests. This is a basic laboratory issue. John is not sure if there are references in the literature on this. Greg said creatinine is stable for 24 hours in whole blood. There is unpublished data on stability, freeze/thaw or plasma serum. Gary said he can add something, too. Greg will send references for whole blood stability. John will write this with Greg and send it to Gary.

- Conclusion number 2 will be changed because this is creatinine clearance.
- Number 5 will be replaced with creatinine measurement.
- Page 25. Is there data on bio variation and GFR? This needs to be cleaned up. The Analytical Performance Specifications Section needs to be moved. The coefficient of variation using iothalmate clearance, etc. needs to be added and Greg said he would do that.
- A caveat needs to be added about children. The problems are bigger in children because their normal values are so low. There was agreement to add information to the Introduction saying that NKDEP recommends the GFR estimate for children should be done using the Cockfroft-Gault equation. This should also be added to the Limitations section. A disclaimer should also be added to the RECOMMENDATIONS saying that the recommendations for "man" apply to adults, not children. Tom suggested the following wording:
    - *At present the MDRD equation is the best equation to use to estimate GFR in the reduced range, but further refinements may occur in the future.*
- Add a statement to the LIMITATIONS saying that the MDRD equation has not been tested in children. Also add that the MDRD equation is best used to estimate GFR of 60 and below due to calibration issues. MDRD is good for estimated GFR of 60 and below although it is good up to 90 if you calibrate. Certain co-morbid conditions such as cardiovascular conditions, anemia, etc. begin at an estimated GFR of 60.
- Gary will add the information on children to the LIMITATIONS. Put units after the recommendations. Put GFR variability if plus or minus x percent. There was consensus to delete LIMITATION number 1.
- There was consensus to combine LIMITATIONS 2 and 3 and to add a LIMITATION about the estimating equation as LIMITATION number 1. It could say these are the limits of the MDRD study estimating equations. It won't give accurate results in people with normal GFRs. Andy suggested adding under the equation limits that the MDRD study equation won't give accurate results in those with extremes of: age, body size, muscle mass or nutritional status. They don't make creatinine
- Add to the LIMITATIONS information on what the total expected error is; however there was another comment that this is in number 5.
- Make sure number 5 says inulin clearance, not creatinine clearance.
- There was some discussion concerning LIMITATION number 6 on medications. Andy said if the closing recommendations are in broad categories, then MDRD can be used. If they are in narrow categories based on studies, then you need to use the methods from those studies. There was consensus to remove number 6 and to add to the recommendations that this issue should be further studied. When laboratories remove bias from creatinine they will report a lower number, which will impact GFR and therefore drug dosing. Greg will write this information to be added.
- LIMITATION number 2 seems unclear. This reads at present:
    - *Little is known about the analytical non-specificity biases found in individual patient samples and quantitatively the magnitude of the impact they have on the accuracy of GFR estimates computed from serum creatinine alone.*
- Non-specificity biases are interferences and this would be a better word to use.
- CONCLUSIONS. Andy suggested adding rationale saying why CONCLUSION number 1 is okay. It is important to recognize the GFR less than 60 because it is the definition of CKD

and clinicians don't need to estimate kidney function in the normal range, so it's important to estimate kidney function less than 60.

- RECOMMENDATIONS: Change number 5 from 2004 to 2005.
- Add information to the INTRODUCTION on kidney disease. Say that the recommendation is to do staging based on GFR. For people with CKD staging is based on GFR. Put in data in the Introduction on staging. Andy can add that for Gary. Andy said we should also add a table with the stages with the corresponding definition of CKD. The first and second stages are different with GFR greater than 90 or 60 to 90 and we are saying they can't do that accurately.
- Add to the CONCLUSIONS that you can't distinguish between stages 1 and 2 based on GFR. The current table 2 with ranges has a clinical use section. Andy could modify this for his use. Andy said he would make these changes now and send them to Gary.
- Add to the RECOMMENDATIONS that when there is a new standard, the laboratories need to recalibrate and use the new method.
- Add to the CONCLUSIONS AND LIMITATIONS to say that the values will go lower and this is an issue for clinical laboratories and for manufacturers as new equations come out. Greg will rewrite this LIMITATION to address these issues. The reference range will be readdressed. The ranges will go lower depending upon the assay; same percent range as in CONCLUSION number 3. Greg will put in LIMITATION number 6.

Timeline:

- Greg will send his comments to Gary this week, and Georgia will send her notes.
- Gary will incorporate the comments by the middle of the week of 10/25 and send to Georgia, who will have a week to review and edit before sending to the group. A near-final version will be circulated around the week of 11/1.
- Group members will send their feedback to Gary.

NIH Evaluation Funding:

- NIH has a set-aside fund it distributes to evaluate programs. Tom would like to get some of that money to evaluate usage of MDRD. He will circulate to the group his ideas for surveying labs in a systematic way, and people can send him feedback on an individual basis.

Next Meeting (in-person):

- Two proposed dates for the next meeting are February 18, 2005 and March 11, 2005.
- Tentative locations are in the Washington, DC, area, possibly in Crystal City or near BWI.
- Members will be polled on which date and location they prefer.
- Draft agenda:

    1. Discuss recommendations for implementation plan for calibration standardization process.
    2. Readjustment of MDRD (and how it fits into the timeline)